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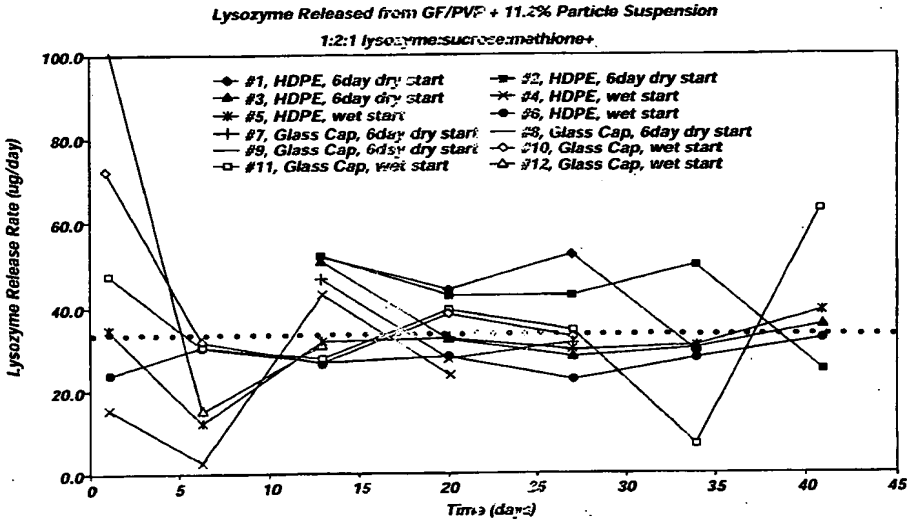

(57) Abstract: The present invention includes materials and methods for providing vehicles useful for providing drug formulations that address the potential drawbacks of known nonaqueous formulations. In particular, the present invention includes nonaqueous vehicles that are formed using a combination of polymer and solvent that results in a vehicle that is miscible in water. The nonaqueous vehicles facilitate the formulation of drug formulations that are stable over time, even when stored at, or exposed to, elevated temperatures. Moreover, the miscible vehicles of the present invention allow the preparation of drug formulations that work to reduce the occurrence of partial or complete occlusions of the delivery conduits included in delivery devices used to administer the drug formulations.

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NON-AQUEOUS SINGLE PHASE VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES

PRIORITY CLAIM

This application claims the benefit of the filing date of United Stats Provisional Patent Application Serial No. 60/459,300, filed March 31, 2003, for "Non-Aqueous Single Phase Vehicles and Formulations Utilizing Such Vehicles."

TECHNICAL FIELD

This invention relates to single-phase vehicles useful in preparing drug formulations. In particular, the invention relates to single-phase vehicles that are nonaqueous, biocompatible, capable of providing a stable suspension of a particulate drug material, and are formulated to facilitate delivery of the drug material at controlled rates over extended periods of time.

BACKGROUND

Implantable devices capable of delivering desired doses of a beneficial agent over extended periods of time are known in the art. For example, U.S. Patent Nos. 5,034,229, 5,557,318, 5,110,596, 5,728,396, 5,985,305, 6,113,938, 6,156,331, 6,375,978, and 6,395,292, teach osmotically driven devices capable of delivering an active agent formulation, such as a solution or a suspension, at a desired rate over an extended period of time (*i.e.*, a period ranging from more than one week up to one year or more). Other exemplary implantable devices include regulator-type implantable pumps that provide constant flow, adjustable flow, or programmable flow of beneficial agent formulations, which are available from, for example, Codman of Raynham, Massachusetts, Medtronic of Minneapolis, Minnesota, and Tricumed Medinzintechnik GmbH of Germany. Further examples of implantable devices are described in U.S. Patent Nos. 6,283,949, 5,976,109, 5,836,935, 5,511,355. Because they can be designed to deliver a desired active agent at therapeutic levels over an extended period of time, implantable delivery systems can advantageously provide long-term therapeutic dosing of a desired active agent

without requiring frequent visits to a healthcare provider or repetitive self-medication. Therefore, implantable delivery devices can work to provide increased patient compliance, reduced irritation at the site of administration, fewer occupational hazards for healthcare providers, reduced waste hazards, and increased therapeutic efficacy through enhanced dosing control.

However, the delivery of beneficial agents that include biomolecular material over an extended period of time using an implantable drug delivery system has proven difficult. As it is used herein, the term "biomolecular material" refers to peptides, polypeptides, proteins, nucleic acids, viruses, antibodies, and any other naturally derived, synthetically produced, or recombinantly produced beneficial agent that includes nucleic or amino acid. The term "biomolecular material" includes lipoproteins and post-translationally modified forms, e.g., glycosylated proteins. The term also includes proteins and/or protein substances which have D-amino acids, modified, derivatized or unnaturally occurring amino acids in the D- or L- configuration and/or peptomimetic units as part of their structure. Among other challenges, two problems must be addressed when seeking to deliver biomolecular material over an extended period of time from an implanted delivery device. First, the biomolecular material must be contained within a formulation that substantially maintains the stability of the material at elevated temperatures (*i.e.*, 37° C and above) over the operational life of the device. Second, the biomolecular material must be formulated in a way that allows delivery of the biomolecular material from an implanted device into a desired environment of operation over an extended period time. This second challenge has proven particularly difficult where the biomolecular material is included in a flowable composition that is delivered from a device over an extended period of time at low flow rates (*i.e.*, $\leq$ 100 µl/day).

Biomolecular material may degrade via one or more of several different mechanisms, including deamidation, oxidation, hydrolysis, disulfide interchange, and racemization. Significantly, water is a reactant in many of the relevant degradation pathways. Moreover, water acts as a plasticizer and facilitates the unfolding and irreversible aggregation of biomolecular materials. To work around the stability problems created by aqueous formulations of biomolecular materials,

dry powder formulations of biomolecular materials have been created using known particle formation processes, such as by known lyophilization, spray-drying, or dessication techniques. Though dry powder formulations of biomolecular material have been shown to provide suitable stability characteristics, it would be desirable to provide a formulation that is not only stable over extended periods of time, but is also flowable and readily deliverable from an implantable delivery device.

In order to provide nonaqueous drug formulations that include biomolecular materials and are deliverable from an implantable device, wherein the biomolecular materials are stable over extended periods of time at elevated temperatures, ALZA Corporation developed the formulations and methods described in International Publication Number WO 00/45790 ("the '790 publication"). The '790 publication describes nonaqueous vehicle formulations that are formulated using at least two of a polymer, a solvent, and a surfactant. The vehicle formulations of the '790 publication are well suited to the preparation of drug suspensions that include biomolecular drug materials and are stable over extended periods of time, even at elevated temperatures. However, under certain circumstances, the formulations taught in the '790 publication may have the potential to inhibit drug delivery into the desired environment of operation. In particular, where the formulations taught in the '790 publication are exposed to an aqueous liquid, such as a physiological fluid, within a delivery conduit of a device used to deliver the formulations, the polymer included in the vehicle tends to phase separate from the solvent into the aqueous liquid. As the polymer partitions into the aqueous liquid, the concentration of polymer within the aqueous liquid may increase to such an extent that a highly viscous polymer gel or precipitate is formed within the delivery conduit, resulting in a partial or complete occlusion of the delivery conduit and interfering with the desired operation of the delivery device. The potential for such occlusions increases where the geometry of the conduit is such that aqueous liquid interfaces with the drug formulation in a confined area over a relatively long period of time (*e.g.*, hours or days).

It would be an improvement in the art to a provide a vehicle that allows the creation of drug formulations that not only facilitate the delivery of biomolecular

materials from an implanted device, but also exhibit a reduced potential for blocking or occluding the delivery conduit of the device from which formulations are delivered. Ideally, such formulations would allow delivery of biomolecular materials from an implanted device at a variety of controlled rates and would work to maintain the stability of the biomolecular materials included therein over extended periods of time, even at elevated temperatures.

DISCLOSURE OF INVENTION

In one aspect, the present invention includes materials and methods for providing vehicles useful for providing drug formulations that address the potential drawbacks of known nonaqueous formulations. In particular, the present invention includes nonaqueous vehicles that are formed using a combination of polymer and solvent that results in a vehicle that is miscible in water. As it is used herein, the term "miscible in water" refers to a vehicle that, at a temperature range representative of a chosen operational environment, can be mixed with water at all proportions without resulting in a phase separation of the polymer from the solvent such that a highly viscous polymer phase is formed. For the purposes of the present invention, a "highly viscous polymer phase" refers to a polymer containing composition that exhibits a viscosity that is greater than the viscosity of the vehicle before the vehicle is mixed with water. Because they do not form a highly viscous polymer phase upon mixture with water, vehicles according to the present invention allow the creation of drug formulations that work to reduce the occurrence of partial or complete occlusions of the delivery conduits included in delivery devices used to administer the formulations.

Though different polymer and solvent combinations may be used to create a vehicle according to the present invention, the polymer and solvent are chosen and combined in a manner that provides a vehicle that is not only miscible with water, but is also suitable for creating a suspension of drug material that works to maintain the stability of the drug, even when the suspension is exposed to elevated temperatures. As it is used herein, the terms "stable" and "stability" refer to both the chemical and physical stability of a drug material. In particular, a formulation is

considered chemically stable according to the present invention if no more than about 35% of the drug substance is degraded by chemical pathways, such as by oxidation, deamidation, and hydrolysis, after maintenance of the formulation at 37° C for a period of two months, and a formulation is considered physically stable if, under the same conditions, no more than about 15% of the drug substance contained in the formulation is degraded through aggregation. A drug formulation is stable according to the present invention if at least about 65% of the drug substance remains physically and chemically stable after about two months at 37° C.

In another aspect, the present invention is directed to a drug formulation that includes a drug dispersed within a vehicle according to the present invention. The drug included in a drug formulation according to the present invention is preferably provided as a particulate material. The particulate material may be substantially pure drug material or may be formed of drug particles that include the drug material plus one or more coatings, preservatives, excipients, or adjuvants. Though vehicles according to the present invention are particularly suited for providing drug formulations that incorporate particulate biomolecular material, the formulations of the present invention are not so limited. As it is used herein, the term "drug" refers to any compound or material that provides a therapeutic or beneficial effect and includes, for example, medicines, vitamins, nutrients, and food supplements. However, in each embodiment of a drug formulation of the present invention, the vehicle is chosen and the particulate drug material is prepared such that the drug is not soluble in one or more of the vehicle components.

In yet another aspect, the present invention includes methods of producing vehicles and drug formulations according to the present invention. In one embodiment, a method of producing a vehicle according to the present invention includes combining the vehicle components and blending such components at elevated temperature until a single-phase material is achieved. A drug formulation according to the present invention is prepared by dispersing a particulate drug material in a vehicle according to the present invention to provide a suspension having a desired distribution of particulate drug material. In one embodiment, a method of preparing a drug formulation according to the present invention includes

mixing a particulate drug material with a vehicle according to the present invention at elevated temperatures until a suspension having a desired distribution of particulate drug material is achieved. Methods for producing a vehicle or a drug formulation according to the present invention are preferably carried out without the addition of water to the ingredients used in forming the vehicle, to the vehicle itself, or to the particulate drug material dispersed within the vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a graph illustrating the release rate performance provided by a lysozyme formulation that was prepared using a vehicle according to an embodiment the present invention and was released from osmotic pumps designed to deliver the lysozyme formulation at a rate of 1.5 µl/day over a three-month period of time, providing a targeted lysozyme release rate of 35 µg/day.

FIG. 2 illustrates the increase in oxidation and deamidation of omega-interferon included in a first exemplary drug formulation prepared according to the present invention (Formulation A), after such formulation was stored at 5° C, 25° C, and 40° C for three months.

FIG. 3 illustrates the increase in oxidation and deamidation of omega-interferon included in a second exemplary drug formulation prepared according to the present invention (Formulation B), after such formulation was stored at 5° C, 25° C, and 40° C for three months.

FIG. 4 illustrates the omega-interferon monomer stability provided by Formulation A and Formulation B after such formulations were stored at 5° C, 25° C, and 40° C for three months.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention includes a vehicle useful for providing nonaqueous drug formulations. A vehicle according to the present invention includes at least a polymer and a solvent combined to provide a single-phase material that is biocompatible, nonaqueous, and miscible with water. Therefore, despite being formulated of one or more polymers and one or more solvents, the polymers and

solvents used in a vehicle according to the present invention are chosen to provide a homogeneous system that is both physically and chemically uniform throughout, as determined by differential scanning calorimetry (DSC). To achieve a biocompatible vehicle, the polymers and solvents used in the vehicle according to the present invention are chosen and combined such that the resultant vehicle disintegrates or breaks down over a period of time in response to a biological environment. The breakdown of the vehicle in a biological environment may take place by one or more physical or chemical processes, such as by enzymatic action, oxidation, reduction, hydrolysis (*e.g.*, proteolysis), displacement, or dissolution by solubilization, emulsion or micelle formation. After a vehicle of the present invention is broken down in a biological environment, components of the vehicle are then absorbed or otherwise dissipated by the body and surrounding tissue.

A vehicle according to the present invention may include any pharmaceutically acceptable polymer that can be combined with a solvent to provide a vehicle that is miscible with water, single-phase, biocompatible, suitable for creating and maintaining drug suspension, and capable of providing a stable drug formulation. Examples of polymers useful in forming a vehicle according to the present invention include, but are not limited to, polyesters such as PLA (polylactic acid) having an inherent viscosity in the range of about 0.5 to 2.0 i.v. and PLGA (polylacticpolyglycolic acid) having an inherent viscosity in the range of about 0.5 to 2.0 i.v., pyrrolidones such as polyvinylpyrrolidone (having a molecular weight range of about 2,000 to 1,000,000), esters or ethers of unsaturated alcohols such as vinyl acetate, and polyoxyethylenepolyoxypropylene block copolymers such as Pluronic 105. If desired, more than one different polymer or grades of single polymer may be used to achieve a vehicle according to the present invention.

The solvent included in a vehicle according to the present invention includes any solvent that is pharmaceutically acceptable and can be combined with a suitable polymer to provide a vehicle that is miscible with an aqueous liquid, single-phase, biocompatible, suitable for creating and maintaining a drug suspension, and capable of providing a stable drug formulation. The solvent may be water soluble, but such a characteristic is not required. For instance, benzyl alcohol (BA) is a solvent that

may be used to provide a miscible vehicle according to the present invention, even though BA itself is not readily soluble in water. Further examples of solvents that may be used to provide a vehicle according to the present invention include, but are not limited to, glycofurol, tetraglycol, n-methylpyrrolidone, glycerol formal, glycerine, and propylene glycol where desired, two or more solvents may be used to provide a vehicle according to the present invention. In particular, two or more solvents may be required to provide a vehicle that is both miscible in water and facilitates the production of a stable formulation of a chosen drug.

A vehicle according to the present invention may be a Newtonian or a non-Newtonian material, and the viscosity of the vehicle will vary. In each embodiment, however, a vehicle according to the present invention is formulated to provide a viscosity that is capable of maintaining a desired suspension of a chosen particulate drug material over a predetermined period of time, thereby facilitating creation of a drug formulation tailored to provide controlled drug delivery at a desired rate. Therefore, the viscosity of a vehicle according to the present invention will vary depending on, among other factors, the desired application, the size and type of the particulate drug material to be included in the vehicle, and the required vehicle loading. The viscosity of a vehicle according to the present invention can be varied, as desired, by altering the type or relative amounts of solvent and polymer materials included in the vehicle. In one embodiment, the vehicle of the present invention is formulated as a viscous vehicle, with the vehicle having a viscosity in the range of about 1,000 to 10,000,000 poise. Where the vehicle of the present invention is formulated as a viscous vehicle, the viscosity of the vehicle preferably ranges from about 10,000 to 250,000 poise. Where viscosities are mentioned herein, they are measured at 37° C at a shear rate of 10^{-4}/sec using a parallel plate rheometer.

The amount of polymer and solvent included in a vehicle according to the present invention may be varied to provide a vehicle having desired performance characteristics. Generally, however, a vehicle according to the present invention will include about 40% to about 80% (wt/wt) polymer and about 20% to about 60% (wt/wt) solvent. Presently preferred embodiments of a vehicle according to the present invention include vehicles formed of polymer and solvent combined at the

following ratios: about 25% solvent and about 75% polymer; about 30% solvent and about 70% polymer; about 35% solvent and about 65% polymer; about 40% solvent and about 60% polymer; about 45% solvent and about 55% polymer; and about 50% solvent and about 50% polymer (with all percentages given in wt/wt ratios). However, it is not necessary that the vehicle of the present invention be formed using only polymer and solvent.

Beyond polymers and solvents, a vehicle according to the present invention may also include one or more surfactants or preservatives. Surfactants that may be used in a vehicle according to the present invention include, but are not limited to, esters of polyhydric alcohols such as glycerol monolaurate, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols such as myristyl lactate (Ceraphyl 50), and polyoxyethylenepolyoxypropylene block copolymers, such as Pluronic. One or more surfactants may be included in a vehicle according to the present invention to facilitate release of the drug from the vehicle once a drug formulation according to the present invention is delivered to an environment of operation. Alternatively, one or more surfactants may be included in a vehicle according to the present invention to help maintain the stability of a drug that is to be suspended therein. Where included, a surfactant will typically account for less than about 20% (wt/wt), with preferred ranges of surfactant being less than about 10% (wt/wt), and less than about 5% (wt/wt). Preservatives that may be used in a vehicle according to the present invention include, for example, antioxidants and antimicrobial agents. Examples of potentially useful antioxidants include, but are not limited to, tocopherol (vitamin E), ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate. Where one or more preservatives are incorporated in a vehicle according to the present invention, the amount used will vary depending on the application, the preservative used, and the desired result. Generally, a preservative is included only in amounts sufficient to achieve the desired preservative effect.

A vehicle according to the present invention is preferably manufactured by combining the desired ingredients without the addition of water. Generally, vehicles according to the present invention may be prepared by combining the dry (*e.g.*,

powdered or low moisture content) ingredients in a dry box or under other dry conditions and blending them at an elevated temperature, preferably about 40° C to about 70° C, to allow them to liquefy and form a single phase. Where a vehicle according to the present invention includes a surfactant, the solvent portion of the vehicle is preferably combined with the surfactant at an elevated temperature before the desired polymer material is added for blending. Blending of the ingredients can be accomplished using any suitable equipment, such as a dual helix blade mixer, and blending is preferably completed under vacuum to remove trapped air bubbles produced from the dry ingredients. Once a liquid solution of the vehicle ingredients is achieved, the liquid vehicle may be allowed to cool to room temperature. If desired, the liquid vehicle may be removed from the blending apparatus to allow for cooling. Differential scanning calorimetry may be used to verify that the components included in the vehicle have been combined such that a single-phase materials is formed. The final moisture content of the vehicle is preferably less than 5%.

The vehicle of the present invention facilitates the manufacture of drug formulations that work to reduce or eliminate the formation of partial or complete occlusions in the delivery channels of devices designed to deliver drug formulations at a controlled rate over an extended period of time, particularly where such devices are implanted or introduced into an environment of operation that includes aqueous liquid. Without being limited to a particular mechanism, it is believed that such performance is due, at least in part, to miscibility of the vehicle with water. Specifically, it is believed that the miscibility of the vehicle of the present invention with water works to reduce or prevent phase separation of the polymer and solvent materials included in the vehicle when the vehicle comes in contact with an aqueous liquid. As a result, where a drug formulation utilizing a vehicle according to the present invention interfaces with an aqueous liquid in a delivery channel of a delivery device, the polymer included in the vehicle exhibits a reduced tendency to partition into the aqueous liquid in a manner that may result in the partial or complete occlusion of the delivery channel by a polymer precipitate.

A drug formulation according to the present invention includes an amount of drug suspended within a vehicle according to the present invention. To create a suspension of drug within a vehicle according to the present invention, the drug is dispersed within a vehicle according to the present invention as a dry particulate material, meaning that the drug is present in a solid state (*e.g.*, a powder, crystalline, or amorphous state). When creating a drug formulation according to the present invention, the vehicle is chosen and the particulate drug material is prepared such that the drug is substantially insoluble in the vehicle. Suitable particulate drug and vehicle combinations can be determined by one of skill in the art on the basis of the solubility characteristics. *See, for example,* Gilman, et. al, The Pharmacological Basis of Therapeutics, 7th ed. (1990) and Remington, Pharmacological Sciences, 18th ed. (1990).

The amount of particulate drug material included in a drug formulation according to the present invention may vary depending on, among other factors, the potency of the drug, the desired duration of treatment, and the desired release rate of drug. Typically, the particulate drug material accounts for between about 0.1% to 50% (w/w) of a drug formulation according to the present invention, with the vehicle accounting for between about 50% and 99.9% (w/w). In preferred embodiments, a drug formulation according to the present invention includes between about 1% and 30% (w/w) particulate drug material.

The drug included in a drug formulation according to the present invention may include any beneficial agent that either exhibits desired solubility characteristics or may be prepared as a particulate material exhibiting desired solubility characteristics. Drugs useful in a drug formulation according to the present invention may be provided in the form of pharmaceutically acceptable salts, including salts with inorganic acids, organic acids, inorganic bases, or organic bases. In one embodiment, the drug included in a drug formulation according to the present invention is a biomolecular material, such as a peptide or protein that has biological activity or that may be used to treat a disease or other pathological condition. Specific examples of peptides or proteins that may be used in a drug formulation according to the present invention include, but are not limited to, adrenocorticotropic

hormone, angiotensin I and II, atrial natriuretic peptide, bombesin, bradykinin, calcitonin, cerebellin, dynorphin N, alpha and beta endorphin, endothelin, enkephalin, epidermal growth factor, fertirelin, follicular gonadotropin releasing peptide, galanin, glucagon, GLP-1, gonadorelin, gonadotropin, goserelin, growth hormone releasing peptide, histrelin, human growth hormone, insulin, interferons, leuprolide, LHRH, motilin, nafarerlin, neurotensin, oxytocin, relaxin, somatostatin, substance P, tumor necrosis factor, triptorelin, vasopressin, growth hormone, nerve growth factor, blood clotting factors, ribozymes, and antisense oligonucleotides. Analogs, derivatives, antagonists, and agonists of the exemplary peptides and proteins described may also be used. Again, however, the drug included in a drug formulation of the present invention is not limited to a biomolecular material. The drug may be any compound or material, including any medicine, vitamin, nutrient, or food supplement, which is capable of providing a therapeutic or beneficial affect when administered to an environment of operation and can be prepared as a particulate material exhibiting desired solubility characteristics.

Any suitable particle formation process may be used to provide the particulate drug material included in a drug formulation according to the present invention. For example, methods that may be used to create the particulate drug material included in a drug formulation of the present invention include, but are not limited to, known spray drying, lyophilization, dessication, granulation, grinding, milling, precipitation, homogenization, or coating processes. Where the process used to create the particulate drug material does immediately result in a dry product, such as is the case with a wet grinding or wet milling process, the particulate drug matter may be dried by any suitable method until a dried product having a desired moisture content is achieved. The particulate drug material included in a drug formulation according to the present invention may consist of substantially pure drug or it may include particles that include the drug and one or more other substances, such as bulking agents, stabilizers, preservatives, coating materials or other adjuvants or excipients that provide a desired particulate drug material. Though in may not be desired or necessary with all such substances, preparing certain drug substances as particulate materials that include one or more stabilizers, bulking

agents, or preservatives can reduce the formation of degradation products (*e.g.*, unstable chemical intermediates). Stabilizers, bulking agents, preservatives, and coating materials, as well as adjuvants or excipients, that may be useful in the formation of a particulate drug material that can be included in a drug formulation according to the present invention are well known in the art. The type and amounts of each such agent will vary depending on, among other factors, the drug to be delivered and the stability and solubility characteristic desired of the particulate drug material.

The particulate drug material included in a drug formulation according to the present invention may be dispersed in a vehicle according the present invention using any mixing, blending, or other dispersion technique that provides a drug formulation having a desired distribution of the particulate drug material. Preferably the particulate drug material is dispersed within the vehicle using a process that does not require the addition of water. For instance, the particulate drug material can be dispersed within a vehicle according to the present invention by combining the vehicle with the particulate drug material under dry conditions and blending the materials under vacuum at an elevated temperature, preferably about 40° C to about 70° C, until a desired dispersion of the particulate drug material within the vehicle is achieved. The particulate drug material and the vehicle may be blended using the same equipment and techniques used to blend the vehicle. In particular, a mixer, such as a dual helix blade or similar mixer, may be used to blend the particulate drug material and vehicle to achieve a drug formulation according to the present invention. After blending at elevated temperatures, the resulting drug formulation is allowed to cool to room temperature. After preparation, a drug formulation of the present invention may be sealed in a dry container to avoid the undesired incorporation of water.

Drug formulations of the present invention are stable when maintained at elevated temperatures and serve to minimize the potential for partial or complete occlusion of the delivery passage of a delivery device from which the formulations are delivered. In preferred embodiments, the drug formulation of the present invention is formulated such that at least about 80% of the drug included in the

formulation remains chemically and physically stable after two months at 40° C. In particularly preferred embodiments, the drug formulation of the present invention is formulated such that more than 90% of the drug included in the formulation remains chemically and physically stable after two months at 40° C, with formulations maintaining the chemical and physical stability of 95% or more of the drug after two months at 40° C being especially desirable. Moreover, drug formulations according to the present invention are preferably formulated such that they remain stable when subjected to sterilization by irradiation (e.g., gamma, beta or electron beam) before exposure to elevated temperatures for an extended period of time. Because they are formed using a vehicle according to the present invention, drug formulations according to the present invention are miscible with aqueous liquid that may be present in the delivery conduit of a delivery device used to administer the drug formulations. Such miscibility works to reduce or eliminate the potential for formation of partial or complete occlusion of the delivery conduit, particularly where the drug formulation is delivered at low rates (*i.e.*, $\leq$ 100 µl/day) and is in contact with an aqueous liquid within the conduit from which the drug formulation is delivered for a long period of time (*i.e.*, about one day or more).

The vehicle and drug formulation according to the present invention may be loaded into, and delivered from, any device capable of delivering a vehicle or drug formulation according to the present invention at a predetermined rate over a desired period of time. For example, vehicles and drug formulations according to the present invention may be delivered from osmotically driven pumps, such as those taught in U.S. Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318, 5,059,423, 5,112,614, 5,137,727, 5151,093, 5,234,692, 5,234,693, 5,279,608, 5,336,057, 5,728,396, 5,985,305, 5,997,527, 5,997,902, 6,113,938, 6,132,420, 6,217,906, 6,261,584, 6,270,787, and 6,375,978. However, the vehicle and drug formulation of the present invention are not limited in application to osmotically driven pumps. For instance, the vehicle and drug formulation according to the present invention may also be delivered using pumps driven by chemical or electromechanical means. Examples of such pumps are well known in the art. Moreover, even though the vehicle and drug formulation of the present invention are

suited to delivery from an implanted device, the vehicle and drug formulation may also be delivered from a device that is not implantable or implanted.

EXAMPLE 1

Three different exemplary vehicles according to the present invention were produced using Glycofurol ("GF") and polyvinylpyrrolidone ("PVP"). The PVP included in each of the three vehicles was obtained from BASF (17 pf) and had a molecular weight below 18,000 MW. The first vehicle included 42% (wt/wt) GF and 58% (wt/wt) PVP. The second vehicle included 40% (wt/wt) GF and 60% (wt/wt) PVP, and the third vehicle included 50% (wt/wt) GF and 50% (wt/wt) PVP. In each instance, the vehicles were created by first charging the raw materials into a mixer. The raw materials were then blended at about 60° C under vacuum (about -27 in Hg) for two hours to achieve a single-phase vehicle. Each of the three vehicles was miscible with water in all proportions.

EXAMPLE 2

A lysozyme formulation according to the present invention was manufactured using the second vehicle of Example 1 and dry, particulate lysozyme material. The lysozyme particles used in the formulation included 1 part lysozyme to two parts sucrose, and 1 part methionine, and the particles were spray dried from a solution including a 25 mM citrate buffer. The simulated drug formulation included 11.2% (wt/wt) lysozyme. The lysozyme formulation was prepared by loading appropriate amounts of the vehicle and the lysozyme particles into a mixer. The particles and vehicle were then blended at about 60° C under vacuum (about -27 in Hg) until a formulation having a substantially uniform suspension of lysozyme particles was achieved.

EXAMPLE 3

The deliverability of the lysozyme formulation of Example 2 was evaluated using two groups of six osmotic pumps. The osmotic pumps were designed to deliver the lysozyme formulation at 1.5 µl/day over a three-month period of time,

providing a targeted lysozyme release rate of 35 µg/day. To evaluate the release rate performance provided by the lysozyme formulation, the osmotic pumps were introduced into an aqueous media that included a phosphate buffer system (PBS) and was maintained at 37° C.

The first group of 6 osmotic pumps was prepared using the following components:

- Reservoir: Titanium alloy
- Piston: C-flex
- Lubricant: silicone medical fluid
- Osmotic Composition: two osmotic tablets (40 mg osmotic engine tablets formed using 76.4% NaCl, 15.5% sodium carboxymethyl cellulose, 6% povidone, 0.5% Mg Stearate, and 1.6% water) + PEG 400 filler
- Semipermeable Membrane: polyurethane polymer, injection molded to desired plug shape
- Diffusion Moderator: high density polyethylene (HDPE) configured to provide a 10 mil spiral delivery conduit having a .25 mm diameter.
- Simulated Drug formulation: 11.2% lysozyme particles (lyso:sucro:meth (1:2:1 and 25 mM citrate) in a vehicle of 60% PVP and 40% GF

To prepare the first group of osmotic pumps, the piston and the inner diameter of the reservoir were first lightly lubricated using the silicon medical fluid. The piston was then inserted ~0.5 cm into the reservoir at the membrane end of the reservoir. An amount of PEG 400 was then introduced into the membrane end of the reservoir and the two osmotic tablets were inserted into the same end to complete the osmotic composition. After insertion of the osmotic engine tablets, the resulting osmotic composition was flush with the membrane end of the reservoir. A semipermeable membrane plug (hereinafter "the membrane plug" or "plug") was inserted into the reservoir by lining up the plug with the membrane end of the

reservoir and pushing gently until the retaining features of the plug were fully engaged in the reservoir. The lysozyme formulation was loaded into a syringe, which was then used to fill the reservoir from the outlet end (opposite the membrane end) by injecting the lysozyme formulation into the reservoir until the formulation was ~3 mm from the end. The filled reservoir was centrifuged (outlet end "up") to remove any air bubbles that trapped in the lysozyme formulation during filling. The diffusion moderator was screwed into the outlet end of the reservoir until completely engaged. As the diffusion moderator was screwed in, excess amount of lysozyme formulation exited out of the delivery conduit, ensuring a uniform fill.

The second group of six osmotic pumps was manufactured using the same components and methods as were used to manufacture the first group of osmotic pumps, except that the second group of osmotic pumps utilized diffusion moderators. Instead of a diffusion moderator formed of an HDPE plug that creates a spiral-shaped delivery, the diffusion moderator included in the second group of osmotic pumps was formed of a .3 mm square glass capillary glued into an HDPE plug. The glass capillary formed a generally straight delivery conduit.

The release rate performance exhibited by each of the osmotic pumps, including both the first group and the second group, is illustrated in FIG. 1. As indicated in the figure, three osmotic pumps from each group were "wet started" and three osmotic pumps from each group were "dry started." As they are used herein, the term "wet start" or "wet started" indicates that the osmotic pumps were primed such that the osmotic pumps were pumping before introduction into the PBS media for release rate testing, and the term "dry start" or "dry started" indicates that the osmotic pumps were not primed before introduction into the PBS media for release rate testing. Priming of the wet started osmotic pumps was carried out simply by positioning the membrane included in the osmotic pumps in PBS media until the osmotic pumps were pumping at a desired rate. After 40 days of operation in the PBS media, each of the twelve osmotic pumps was still functioning and, in general, delivering amounts of lysozyme that were at or near the targeted delivery rate.

EXAMPLE 4

Additional vehicles according to the present invention were prepared and their miscibility characteristics were evaluated. Four different vehicles including benzyl alcohol ("BA") as a solvent and PVP as a polymer were prepared. Two different grades of PVP (12 pf and 17 pf) from BASF were used in the preparation of these vehicles. The first vehicle included 40% (wt/wt) BA and 60% (wt/wt) PVP 17 pf. The second vehicle included 38% (wt/wt) BA and 62% (wt/wt) PVP 17 pf. The third vehicle included 26% (wt/wt) BA, 37% (wt/wt) PVP 12 pf, and 37% (wt/wt) PVP 17 pf, and the fourth vehicle included 27% (wt/wt) BA, 36.5 % (wt/wt) PVP 12 pf and 36.5% (wt/wt) PVP 17 pf. In each instance, the vehicles were created by first charging the raw materials into a mixer. The raw materials were then blended at 50° C under vacuum (about -28 in Hg) for 60 to 90 minutes, resulting in single-phase vehicles according to the present invention.

Each of the four BA/PVP vehicles prepared according to this Example exhibited desirable miscibility characteristics. To evaluate the miscibility characteristics of these vehicles, water or a phosphate buffer solution was added to each vehicle in varying amounts to determine when, or if any, phase separation could be observed. With each of the four vehicles prepared, no phase separation was observed until the water or phosphate buffer content increased to 50% or more, at which point the PVP included in the vehicle was too dilute to precipitate or form a highly viscous polymer material.

EXAMPLE 5

Yet another exemplary vehicle was prepared according to the method described in Example 4, except that the vehicle was formulated using 36% (wt/wt) BA, 32% (wt/wt) PVP 12 pf, and 32% (wt/wt) PVP 17 pf. The miscibility characteristics of lysozyme formulations prepared using this vehicle were then evaluated.

Four different lysozyme formulations were prepared. Each of the formulations were prepared using the vehicle prepared in this example as well as one of four different particulate lysozyme compositions. The particulate lysozyme

compositions were prepared by spray-drying lysozyme formulations prepared using a citrate buffer. The particles of the first particulate lysozyme composition included 1 part lysozyme to 2 parts sucrose. The particles of the second particulate composition included 1 part lysozyme to 2 parts sucrose and 1 part methionine. The particles of the third particulate lysozyme composition included 1 part lysozyme to 3 parts sucrose and 1 part dextran, and the particles of the fourth particulate lysozyme composition included 1 part lysozyme to 3 parts sucrose, 1 part methionine, and 1 part dextran. To prepare each of the four lysozyme formulations, a vehicle prepared according to this example was combined with each of the four particulate lysozyme compositions such that, in each case, a substantially uniform suspension having 10% particle loading was achieved. Blending of the particulate lysozyme compositions and the vehicle was carried out at 60° C under vacuum (about -28 in Hg).

Once each of the four lysozyme formulations were prepared, a phosphate buffer solution was added to each and the phase behavior of the four formulations was observed. As was true of the vehicles prepared in Example 4, the four lysozyme formulations exhibited desirable miscibility characteristics. With each of the four lysozyme formulations, no phase separation was observed until the phosphate buffer content increased to 50% or more, at which point the PVP included in the vehicle was too dilute to precipitate or form a highly viscous polymer material.

EXAMPLE 6

The stability of an exemplary drug incorporated in drug formulations according to the present invention was evaluated. To evaluate the stability of a drug formulation according to the present invention, two different drug formulations were prepared and stored in titanium reservoirs over a period of three months at a temperature of 5° C, 25° C, or 40° C. After storage of the drug formulations over the three-month period, the stability of the drug included in each formulation was evaluated using reverse phase, high performance liquid chromatography (RP-HPLC) and size exclusion chromatography (SEC).

The drug used in both drug formulations of this example was omega-interferon. The omega-interferon was prepared as a particulate composition,

which included particles formulated to include 1 part omega-interferon to 2 parts sucrose and 1 part L-methionine. The omega-interferon particles were spray dried from a formulation including 25 mM citrate buffer, and as a result, the omega-interferon particles formed also included 7 parts citrate for every 4 parts omega-interferon. In preparing the formulation to be spray dried, a 2% solids content was targeted. When spray drying the omega-interferon particles, a pump rate of 4 ml/min was used. The inlet temperature was 120° C, and the outlet temperature was 85° C.

The vehicle used in both drug formulations included 40% BA and 60% PVP 17 pf. Before blending, however, both the BA and PVP materials were processed to remove peroxides to a level of less than 5 ppm. To remove peroxides from the BA material, alumina was mixed with the BA for 30 minutes, after which the BA was filtered through a 0.2μ filter and stored in a sealed vial under nitrogen. To remove peroxides from the PVP material, the PVP was treated with 1% L-methionine solution, diafiltered using a Millipore TTF system to remove residual L-methionine, and lyophilized. Peroxide levels in the processed BA and PVP materials were measured using an OXIS test kit, and moisture levels in the processed materials were measured using Karl Fisher titration. Both the BA and the PVP were processed to achieve moisture levels below 3% and peroxide values below 5 ppm. After suitable moisture content and peroxide levels were achieved, suitable amounts of the processed BA and PVP were charged into a mixer and blended at 50° C under vacuum (-28 in Hg), until a single-phase vehicle was formed (typically, 60 to 90 minutes). After blending, the moisture content and the peroxide level of the vehicle was confirmed to be less than 3% and less than 5 ppm, respectively.

Both the first and the second formulations were formed using the vehicle and omega-interferon particles described in this Example. However, the two drug formulations were prepared with different amounts of particulate omega-interferon. The first drug formulation (Formulation A) was prepared with a particle loading of 9.6% (wt/wt) and the second drug formulation (Formulation B) was prepared with a particle loading of 3.8% (wt/wt), with the vehicle accounting for the remainder of the formulation in each instance. To prepare the drug formulations, appropriate

amounts of the omega-interferon particles and the vehicle were loaded into a mixer and mixed at 60° C under vacuum (-28 in Hg), until a substantially uniform suspension of the omega-interferon particles was achieved in the vehicle. After mixing, the resulting drug formulations were placed in an oven at 50° C and subjected to a vacuum to remove residual air bubbles that may have been blended into the drug formulations as a result of the mixing.

To evaluate the stability of the drug formulations prepared, the formulations were loaded into titanium reservoirs that were lubricated with silicon medical fluid and sealed with fluoroelastomer pistons. Formulation A and Formulation B were loaded into titanium reservoirs that were stored for 3 months at 5° C, 25° C, and 40° C. After storage of the exemplary drug formulations in the titanium reservoirs at the designated temperature conditions, the degradation of omega-interferon by oxidation and deamidation was evaluated using HPLC, and the degradation of omega-interferon by aggregation was evaluated using SEC. The results of the study are illustrated in FIG. 2, FIG. 3, and FIG. 4.

FIG. 2 illustrates the increase in oxidation and deamidation of the omega-interferon that occurred in Formulation A during storage of the formulation in the titanium reservoirs at the designated temperatures. As can be appreciated by reference to FIG. 2, Formulation A provided desirable stability characteristics. In particular, even after storage of Formulation A at 40° C for three months, oxidation of the drug increased approximately 0.25% and deamidation of the drug increased less than 0.5%.

FIG. 3 illustrates the increase in oxidation and deamidation of the omega-interferon that occurred in Formulation B during storage of the formulation in the titanium reservoirs at the designated temperatures. As can be appreciated by reference to FIG. 3, Formulation B also provided desirable stability characteristics. Even after storage of Formulation B at 40° C for three months, oxidation of the drug increased approximately 0.25% and deamidation of the drug increased approximately 1.3%.

FIG. 4 illustrates the amount of aggregates formed in both Formulation A and Formulation B when stored in titanium reservoirs at the designated temperatures

over the three-month period of time. As can be appreciated by reference to FIG. 4, Formulation A and Formulation B again exhibited desirable stability characteristics, with no significant amounts of drug aggregation occurring in either formulation, even after storage for three months at 40° C.

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CLAIMS

What is claimed is:

1. A stable nonaqueous drug formulation comprising:

at least one drug; and

a nonaqueous, single-phase vehicle comprising at least one polymer and at least one solvent, the vehicle being miscible in water, wherein the drug is insoluble in one or more vehicle components and the drug formulation is stable at 37° C for at least two months.

2. The stable nonaqueous drug formulation according to claim 1, wherein less than about 35% of the drug is degraded by chemical pathways.

3. The stable nonaqueous drug formulation according to any preceding claim, wherein less than about 15% of the drug is degraded through aggregation.

4. The stable nonaqueous drug formulation according to any preceding claim, wherein the drug comprises a particulate material.

5. The stable nonaqueous drug formulation according to any preceding claim, wherein the drug comprises medicines, vitamins, nutrients, or food supplements.

6. The stable nonaqueous drug formulation according to any preceding claim, wherein the drug comprises a peptide or protein.

7. The stable nonaqueous drug formulation according to any preceding claim, wherein the drug is selected from the group consisting of adrenocorticotropic hormone, angiotensin I and II, atrial natriuretic peptide, bombesin, bradykinin, calcitonin, cerebellin, dynorphin N, alpha and beta endorphin, endothelin, enkephalin, epidermal growth factor, fertirelin, follicular gonadotropin releasing

peptide, galanin, glucagon, GLP-1, gonadorelin, gonadotropin, goserelin, growth hormone releasing peptide, histrelin, human growth hormone, insulin, interferons, leuprolide, LHRH, motilin, nafarerlin, neurotensin, oxytocin, relaxin, somatostatin, substance P, tumor necrosis factor, triptorelin, vasopressin, growth hormone, nerve growth factor, blood clotting factors, ribozymes, and antisense oligonucleotides.

8. The stable nonaqueous drug formulation according to any preceding claim, wherein the at least one polymer is selected from the group consisting of polyesters, pyrrolidones, esters of unsaturated alcohols, ethers of unsaturated alcohols, polyoxyethylenepolyoxypropylene block copolymers, and combinations thereof.

9. The stable nonaqueous drug formulation according to any preceding claim, wherein the at least one solvent is selected from the group consisting of glycofurol, tetraglycol, n-methylpyrrolidone, glycerol formal, glycerine, propylene glycol, and combinations thereof.

10. The stable nonaqueous drug formulation according to any preceding claim, wherein the vehicle has a viscosity in the range of about 1,000 to about 250,000 poise when measured at 37° C at a shear rate of 10^{-4}/sec using a parallel plate rheometer.

11. The stable nonaqueous drug formulation according to any preceding claim, wherein the vehicle comprises about 40% to about 80% (wt/wt) polymer and about 20% to about 60% (wt/wt) solvent.

12. The stable nonaqueous drug formulation according to any preceding claim, wherein the vehicle exhibits a moisture content of less than 5%.

13. The stable nonaqueous drug formulation according to any preceding claim, wherein the vehicle comprises glucofurol as a solvent and polyvinylpyrrolidone as polymer.

14. The stable nonaqueous drug formulation according to any preceding claim, wherein the vehicle comprises benzyl alcohol as a solvent and polyvinylpyrrolidone as polymer.

15. A drug delivery device comprising:
a reservoir having at least one drug delivery orifice; and
a stable nonaqueous drug formulation according to any one of claims 1 to 15.

16. The drug delivery device of claim 15, wherein the device is an implantable osmotic pump and the reservoir comprises an osmotic agent.

17. The drug delivery device according to claim 15 or 16, wherein the device is configured to deliver the drug formulation at a rate of less than 100 microliters per day.

18. The drug delivery device according to claims 15 to 17, wherein the device is configured to deliver the drug formulation during a period of time greater than one day.

19. A method for preparing a stable nonaqueous drug formulation according to any one of claims 1 to 15, comprising:
providing a nonaqueous, single-phase vehicle comprising at least one polymer and at least one solvent, the vehicle being miscible in water;
providing a dry, particulate drug material, wherein the drug material is insoluble in one or more vehicle components; and
mixing the drug material with the vehicle to form a drug formulation that is stable at 37° C for at least two months.

20. The method according to claim 19, wherein providing a dry, particulate drug material comprises providing a drug material that has undergone spray drying, lyophilization, dessication, granulation, grinding, milling, precipitation, homogenization, or coating processes.

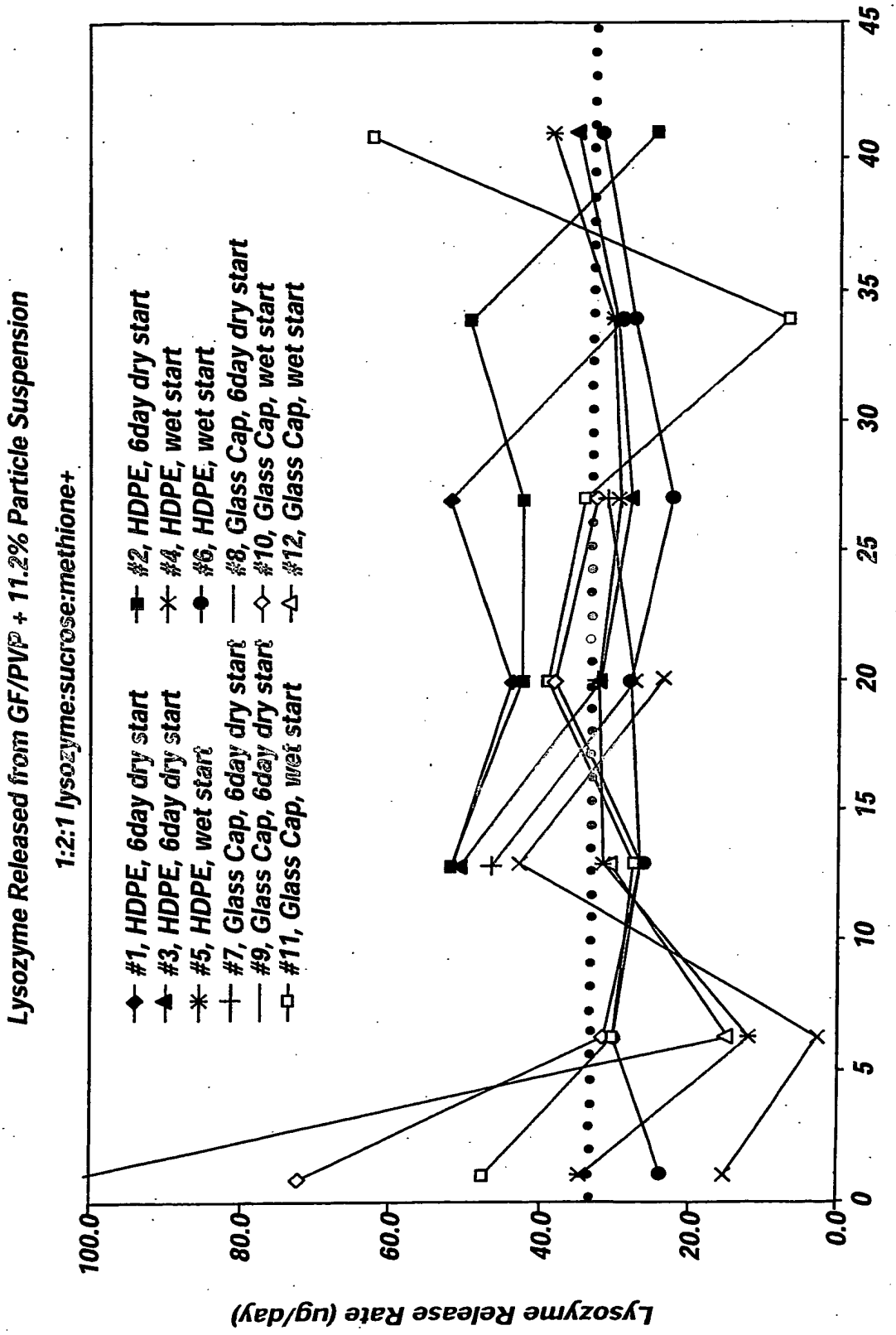
Lysozyme Released from GF/PVP + 11.2% Particle Suspension
1:2:1 lysozyme:sucrose:methione+
#1, HDPE, 6day dry start
#2, HDPE, 6day dry start
#3, HDPE, 6day dry start
#4, HDPE, wet start
#5, HDPE, wet start
#6, HDPE, wet start
#7, Glass Cap, 6day dry start
#8, Glass Cap, 6day dry start
#9, Glass Cap, 6day dry start
#10, Glass Cap, wet start
#11, Glass Cap, wet start
#12, Glass Cap, wet start
Lysozyme Release Rate (ug/day)
100.0
80.0
60.0
40.0
20.0
0.0
0
5
10
15
20
25
30
35
40
45
Time (days)

FIG. 1

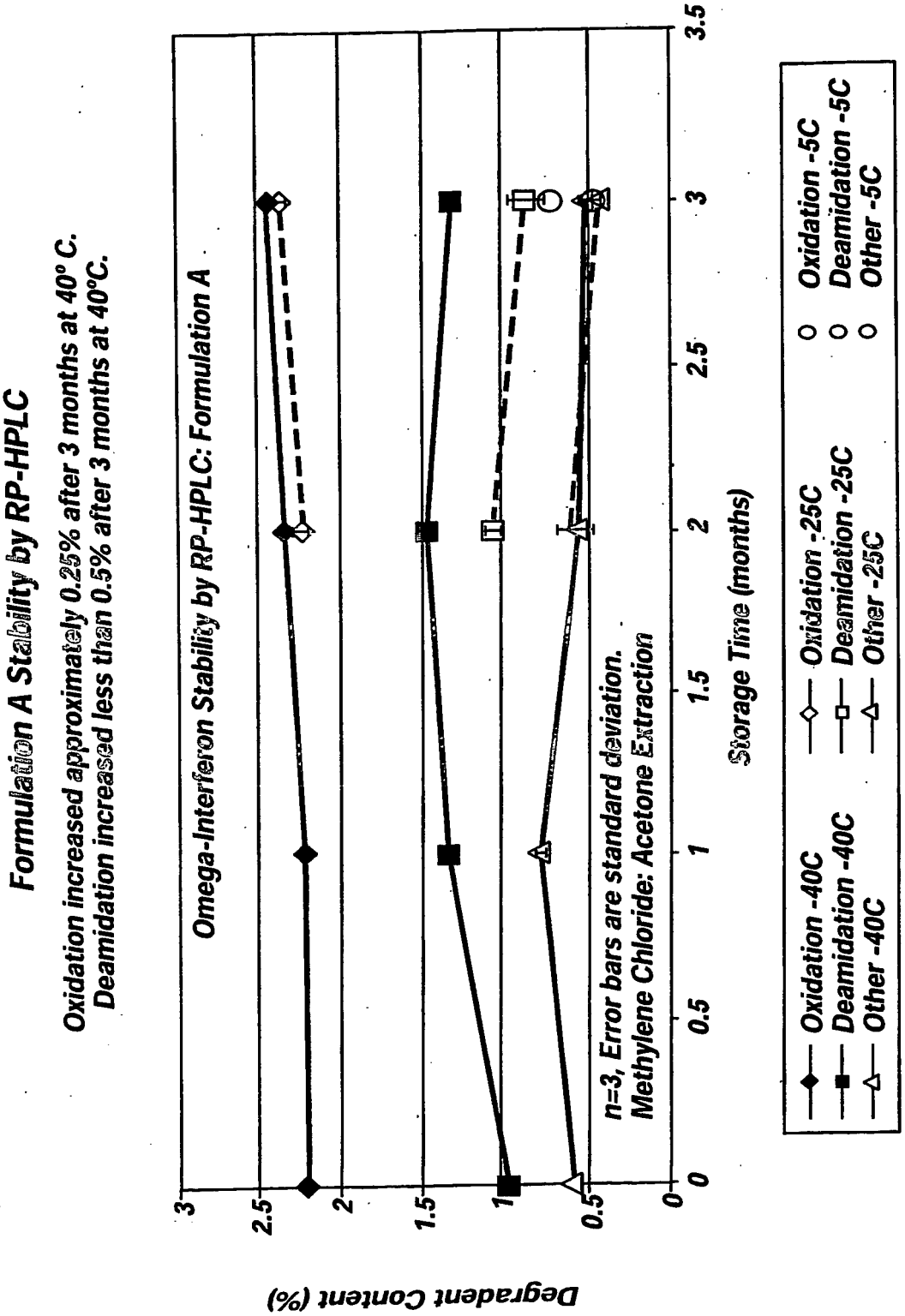

FIG. 2

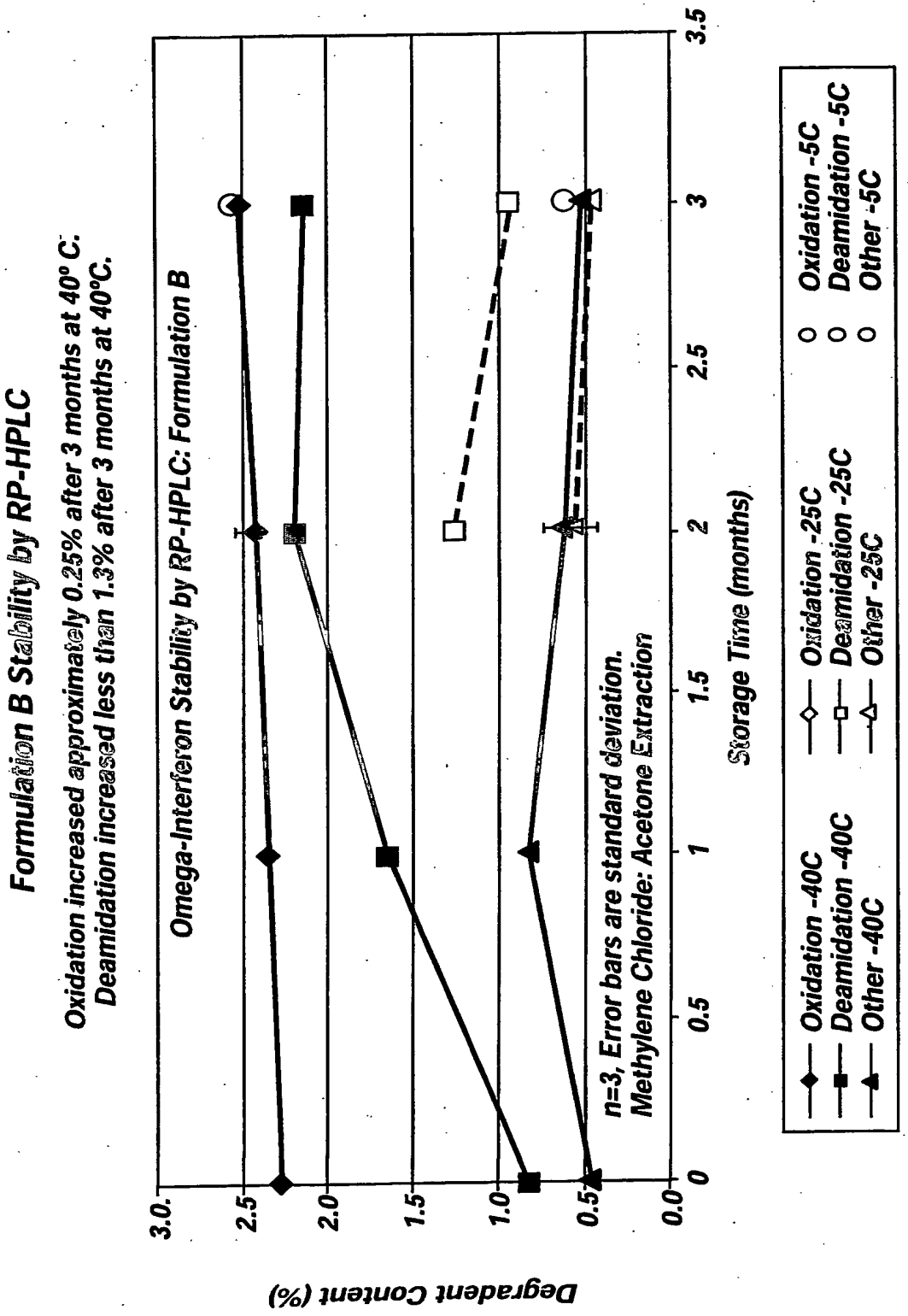
Formulation B Stability by RP-HPLC
Oxidation increased approximately 0.25% after 3 months at 40° C.
Deamidation increased less than 1.3% after 3 months at 40°C.
Omega-Interferon Stability by RP-HPLC: Formulation B
n=3, Error bars are standard deviation.
Methylene Chloride: Acetone Extraction
Degradent Content (%)
Storage Time (months)
Oxidation -40C
Deamidation -40C
Other -40C
Oxidation -25C
Deamidation -25C
Other -25C
Oxidation -5C
Deamidation -5C
Other -5C

FIG. 3

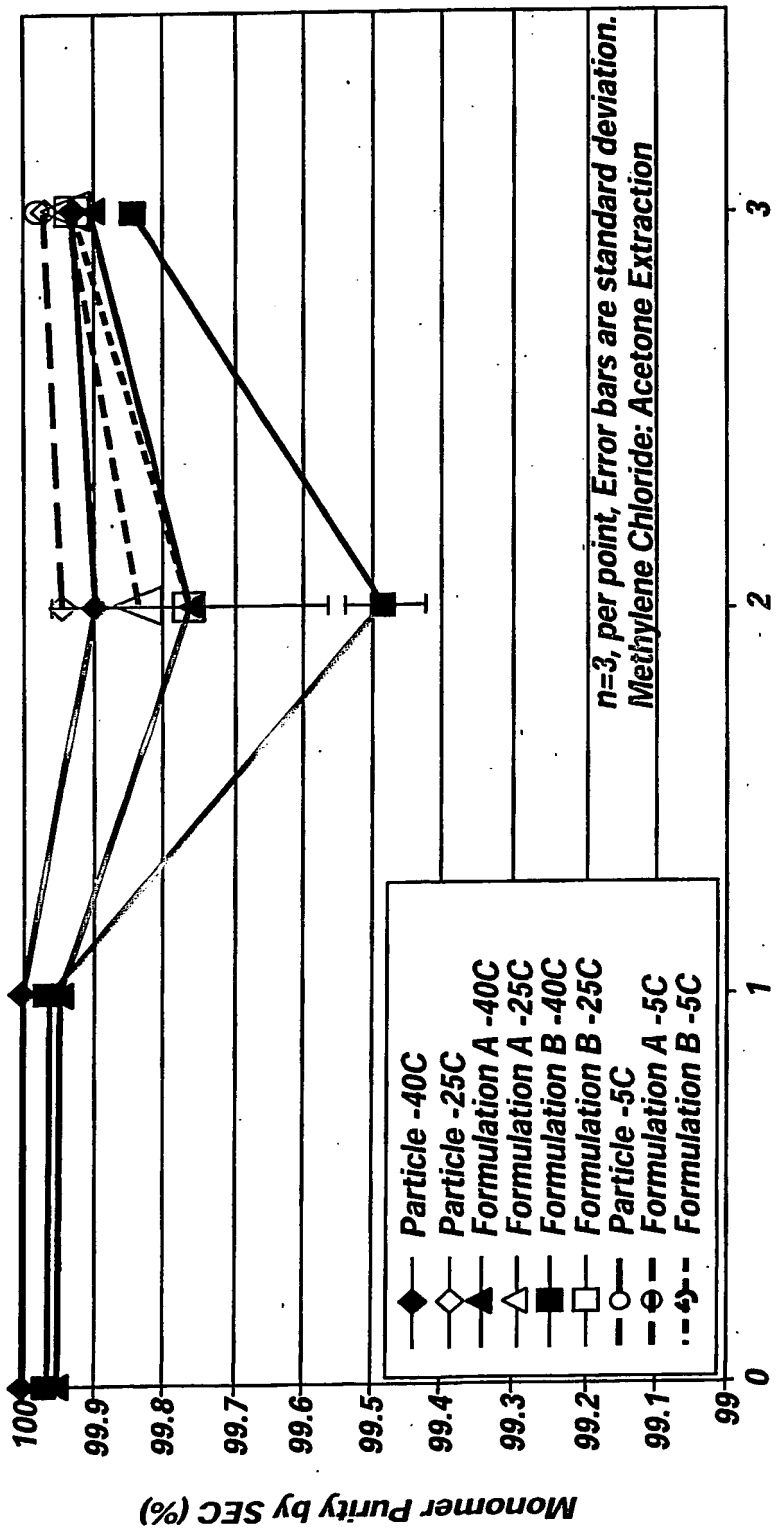

FIG. 4

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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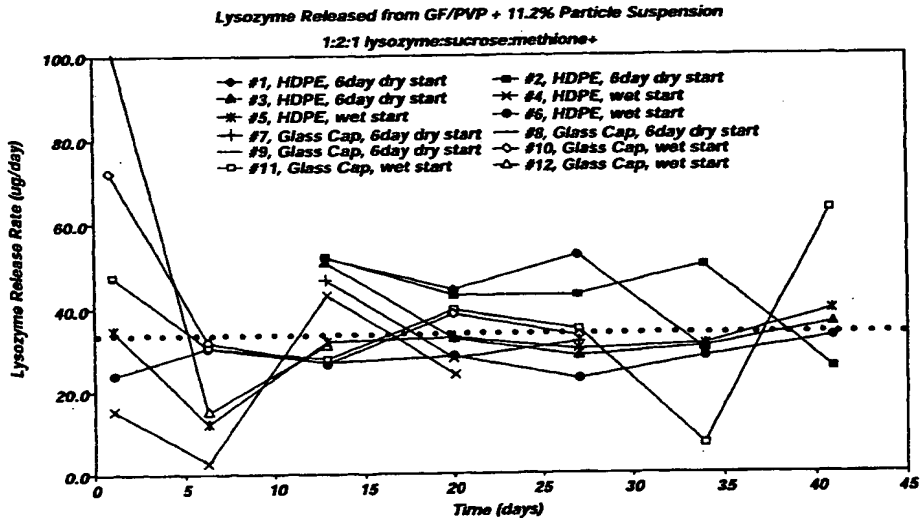
[Continued on next page]

(54) Title: NON-AQUEOUS SINGLE PHASE VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES



(57) Abstract: The present invention includes materials and methods for providing vehicles useful for providing drug formulations that address the potential drawbacks of known nonaqueous formulations. In particular, the present invention includes nonaqueous vehicles that are formed using a combination of polymer and solvent that results in a vehicle that is miscible in water. The nonaqueous vehicles facilitate the formulation of drug formulations that are stable over time, even when stored at, or exposed to, elevated temperatures. Moreover, the miscible vehicles of the present invention allow the preparation of drug formulations that work to reduce the occurrence of partial or complete occlusions of the delivery conduits included in delivery devices used to administer the drug formulations.

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PCT/US2004/009755

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K47/10 A61K47/22 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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12 November 2004	22/11/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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